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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/386,266	08/31/1999	DAVID J. BRAYDEN	99 1080.US	1219

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant
09/386,266	Brayden
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Jan 11, 2002* .

2a) [X] This action is **FINAL.** 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-6 and 15-20* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-6 and 15-20* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) [X] Notice of References Cited (PTO-892)

16) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13*

18) [ ] Interview Summary (PTO-413) Paper No(s)

19) [ ] Notice of Informal Patent Application (PTO-152)

20) [ ] Other:

DETAILED ACTION

Applicant's Amendment

1) Acknowledgment is made of Applicant's amendment filed 01/11/02 (paper no. 11) in response to the non-final Office Action mailed 06/22/01 (paper no. 8), which amendment has been entered. With this, Applicant has amended the specification and the drawings.

Status of Claims

2) No claims have been amended or canceled via the amendment filed 01/11/02.

Claims 1-6 and 15-20 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Information Disclosure Statement

5) Acknowledgment is made of Applicant's information disclosure statement filed 03/26/02 (paper no. 13). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 14).

Objection(s) Withdrawn

6) The objection to the drawings made in paragraph 4 of the Office Action mailed 06/22/01 (paper no. 8) is withdrawn. The amended drawings submitted 01/11/02 (paper no. 12) have been approved by the Draftsperson.

7) The objection to the specification made in paragraph 6 of the Office Action mailed 06/22/01 (paper no. 8) is withdrawn in light of Applicant's amendment to the specification.

Rejection(s) Withdrawn

8) The rejection of claims 1-4, 6 and 15-18 made in paragraph 9 of the Office Action mailed 06/22/01 (paper no. 8) under 35 U.S.C § 102(b) as being anticipated by, or in the alternative,

under 35 U.S.C. § 103(a) as being unpatentable over Jackson *et al.* (*Ann. N. Y. Acad. Sci.* 730: 217-234, 1994), is withdrawn.

9) The rejection of claims 5 and 19 made in paragraph 10 of the Office Action mailed 06/22/01 (paper no. 8) under 35 U.S.C § 103(a) as being unpatentable over Jackson *et al.* (*Ann. N. Y. Acad. Sci.* 730: 217-234, 1994) as applied to claims 1 and 15, and further in view of Mills *et al.* (*Infect. Immun.* 61: 399-410, 1993), is withdrawn.

10) The rejection of claims 1-6 and 15-19 made in paragraph 11 of the Office Action mailed 06/22/01 (paper no. 8) under 35 U.S.C § 103(a) as being unpatentable over Tice *et al.* (US 6,024,983) or Cahill *et al.* (*Vaccine* 13: 455-462, 1995), is withdrawn.

11) The rejection of claim 20 made in paragraph 12 of the Office Action mailed 06/22/01 (paper no. 8) under 35 U.S.C § 103(a) as being unpatentable over Tice *et al.* (US 6,024,983) as applied to claim 15, and in view of Jones *et al.* (*J. Biotechnol.* 44: 29-36, 1996), is withdrawn.

Rejection(s) under 35 U.S.C. § 102

12) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (**b**) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13) Claims 1-4, 6 and 15-18 are rejected under 35 U.S.C § 102(b) as being anticipated by Moore *et al.* (*Vaccine* 13: 1741-1749, 1995).

It is noted that the specification on page 11 at lines 3-6 describes that 'polarization of the immune response may be characterized by determination of the **relative** proportions of T_H1 and T_H2 indicators, typically cytokines such as **IFN-gamma**, TNF, IL-2 or IL-12 and IL-5, IL-4, IL-6 or IL-10 specific to T_H1 and T_H2 responses respectively' [Emphasis added].

Moore *et al.* teach a formulation comprising a recombinant HIV envelope protein antigen, HIV gp120, entrapped in biodegradable poly(lactide-co-glycolide) (PLG, a copolymer of lactic acid and glycolic acid) microparticles suspended in PBS (i.e., pharmaceutically acceptable carrier). The HIV gp120 entrapped PLG microparticles had a mean diameter in the range of 369-501 nm, i.e., less than 3 or 5 micrometer present in at least 50% amount. See abstract; and the first two paragraphs under 'Materials and Methods'. The microparticles are formed by polyvinyl

alcohol (i.e., solvent) evaporation method (see last paragraph in left column on page 1742). Moore *et al.* teach a method of intraperitoneal or subcutaneous administration of 0.2 ml of the gp120 antigen- entrapped PLG in PBS to mice (see the section 'Mouse immunization'). The method induced HIV-specific T-cell responses, HIV envelope-specific CTL responses and T cells that secreted high levels of IFN-gamma and significantly elevated systemic levels of specific IgG (see Figure 1, left panels; Figures 3-5; Tables 1 and 2; 'RESULTS'; and page 1747, left column, first full paragraph). By producing a relatively high concentration of IFN-gamma and low or undetectable IL-4 and IL-5, which is a cytokine profile characteristic of Th1 cells, several mice immunized with gp120 microparticles parenterally showed a "shift in the T-cell response from Th2 to Th1" (i.e., a TH1 polarized response), reflecting the facilitated uptake and presentation particulate antigen by phagocytic cells. Moore *et al.* concluded that immunization using the gp 120 microparticles by the intraperitoneal route favored the induction of Th1 cells (see page 1747, left column, lines 21-34).

Claims 1-4, 6 and 15-18 are anticipated by Moore *et al.*

14) Claims 1-4, 6 and 15-18 are rejected under 35 U.S.C § 102(b) as being anticipated by Nixon *et al.* (*Vaccine* 14: 1523-1530, 1996) as evidenced by Garcon *et al.* (US 6,372,227) or Rook *et al.* (US 6,056,964).

It is noted that the instant specification on page 11, lines 3-6 describes that T_H1 polarized immune response is characterized by the determination of specific IFN-gamma and IL-2.

Nixon *et al.* teach a method of parenteral administration to mice of a composition comprising a microbial peptide antigen entrapped in microparticles comprising poly(lactide-co-glycolide) polymers, sized <500 nm (i.e., less than 3 μm or 5 μm). The composition elicited a better cytotoxic T cell activity (CTL) compared to the composition comprising the peptide antigen entrapped in larger sized microparticles (see abstract; and page 1524, right column under 'Immunization and *in vitro* CTL stimulation'). Small microparticles 450-600 nm in size and medium microparticles of 1.21 μm in size were included in a comparative study wherein lipopeptide antigens entrapped in microparticles of different sizes were studied for their ability to induce CTL (see page 1524, left column below Table 1; and right column under

'Microparticles'). The size of the small microparticles ranged between 450-600 nm and therefore, at least 50% of the microparticles were less than 3 or 5 μm in size. That the microparticles were formed by solvent evaporation is evident from the description provided under the section 'Microparticles' on page 1524. Mice were immunized i.p. or intraperitoneally, or s.c. or subcutaneously (i.e., parenterally) with microgram amounts (i.e., pharmaceutically effective amounts) of the microparticulate immunogen (i.e., entrapped or encapsulated immunogen) suspended in PBS (i.e., pharmaceutically acceptable carrier). See page 1524, right column under 'Immunization and *in vitro* CTL stimulation'; and Figure 4 legend. Nixon *et al.* expressly suggest having in a vaccine composition microparticles prepared from combinations of polymers designed to degrade at different rates after immunization (see page 1530, second full paragraph). Nixon *et al.* expressly teach that microparticles can be used to deliver a mixture of multiple immunogens in a single shot (see page 1529, left column, lines 3-6).

That the prior art method induced T_H1 polarised immune response to the peptide antigen is inherent from the teachings of Nixon *et al.* in light of what is known in the art. For instance, Garcon *et al.* teach that CTL induction correlates with Th-1 cytokine profile responses, specifically IFN-gamma and IL-2 secretion (see lines 37-39 in column 1). Similarly, Rook *et al.* teach the association between TH1 response, production of IL2, IFN-gamma and CTLs and down-regulation of TH2 cell production, and the generation of CTLs driven predominantly by TH1 responses (see column 1, lines 20-24; and column 2, first full paragraph). The disclosure of Nixon *et al.* anticipates the instant claims. Garcon *et al.* or Rook *et al.* is **not** used as a secondary reference in combination with Nixon *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Nixon *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

The induction of a TH1 polarized immune response by the prior art vaccine in the method disclosed is inherent from the teaching of Nixon *et al.* Although the prior art reference does not expressly recite the induction of a TH1 polarized immune response by the vaccine in the disclosed method, the vaccine formulation and the method of Nixon *et al.* are viewed as the same as the instantly claimed vaccine formulation and method. Since the prior art vaccine formulation is structurally the same as the formulation recited in the instant claims and since the prior art

method of parenteral administration of the vaccine formulation is the same as the instantly claimed method, the prior art formulation and the method are expected to, or necessarily result in the same effects, i.e., induction of a T_H1 polarized immune response to the *B. pertussis* antigen.

Claims 1-4, 6 and 15-18 are anticipated by Nixon *et al.*

Rejection(s) under 35 U.S.C. § 103

15) Claims 1, 5, 15 and 19 are rejected under 35 U.S.C § 103(a) as being unpatentable over Moore *et al.* (*Vaccine* 13: 1741-1749, 1995) in view of Locht *et al.* (WO 95/28486).

The teachings of Moore *et al.* are explained above, which do not expressly disclose a vaccine formulation comprising a *Bordetella pertussis* antigen entrapped in their biodegradable polymer and a method of administering the same parenterally.

However, Moore *et al.* expressly teach that induction of predominantly Th1 cells is critical in immune protection against *Bordetella pertussis,* and that immunization with purified soluble protein antigens induces Th2 cells with poor protective efficacy. Moore *et al.* further expressly recommend presentation of such purified soluble recombinant protein antigens (i.e., non-cellular proteins) in a particulate formulation, such as entrapment in biodegradable microparticles, as an ideal approach for the generation of predominantly Th1 cells that play a central role in the protective mechanism (see page 1747, left column, lines 34-48).

Locht *et al.* teach the production of a recombinant *B. pertussis* FHA protein antigen (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the recombinant HIV gp 120 antigen in Moore's formulation and Moore's method of parenteral immunization with Locht's recombinant FHA antigen of *B. pertussis* to produce the vaccine formulation and the method of the instant invention, with a reasonable expectation of success, because Moore *et al.* expressly recommend the entrapment of purified soluble recombinant protein antigens in particulate biodegradable microparticles as an ideal approach for the generation of predominantly Th1 cells that play a central role in the protective mechanism against *B. pertussis*. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of generating predominantly Th1 cells or

immune responses that are known in the art to be central or critical in immune protection against *B. pertussis* as taught by Moore *et al.*

Claims 1, 5, 15 and 19 are *prima facie* obvious over the prior art of record.

16) Claims 1, 5, 15 and 19 are rejected under 35 U.S.C § 103(a) as being unpatentable over Nixon *et al.* (*Vaccine* 14: 1523-1530, 1996) as evidenced by Rook *et al.* (US 6,056,964) and in view of Jones *et al.* (*Behring Inst. Mitt.* 98: 220-228, February 1997) (Jones, 1997) and Mills *et al.* (*Infect. Immun.* 61: 399-410, 1993, already of record).

The reference of Rook *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Nixon *et al.* as evidenced by Rook *et al.* are explained above which do not disclose the use of a *B. pertussis* antigen entrapped or encapsulated in their biodegradable polymer and their method of administration.

However, the use of a *B. pertussis* antigen, such as a fimbrial antigen, encapsulated in biodegradable PLG microparticles and its parenteral administration was well known in the art. For instance, Jones *et al.* (1997) disclosed the use of a pharmaceutical formulation comprising 10 micrograms (i.e., a pharmaceutically acceptable amount) of *B. pertussis* fimbrial antigen encapsulated in biodegradable PLG, i.e., poly(DL-lactide-co-glycolide) microparticles and a method of intraperitoneal (i.e., parenteral) immunization of mice with the same. See section ii) of Jones *et al.* (1997) on pages 223 and 224. This parenteral immunization process resulted in elevated or predominant serum IgG immune response to the antigen (see Figure 2).

Furthermore, the critical role of Th1 immune response in protective immunity to whooping cough and the need for induction of such a response to *B. pertussis* antigen(s) was also well known in the art. For instance, Mills *et al.* taught *B. pertussis* antigen(s) and the need for inducing cellular immune responses mediated by Th1 cells to elicit protective immunity to *B. pertussis* infection (see 'Materials and Methods' and first paragraph under 'Discussion').

Given the art-known use of a *B. pertussis* antigen encapsulated in biodegradable PLG microparticles for parenteral administration to elicit elevated levels of specific serum IgG response as taught by Jones *et al.* (1997), it would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to replace Nixon's antigen with Jones' *B.*

pertussis fimbrial antigen to produce the instant invention, with a reasonable expectation of success. The induction of a TH1 polarized immune response by the prior art vaccine in the method disclosed is implicit from the teaching of Nixon *et al.* as modified by Jones *et al.* (1997) and Mills *et al.* Although the prior art references do not expressly recite the induction of a TH1 polarized immune response by the vaccine in the disclosed method, the vaccine formulation and the method of Nixon *et al.* as modified by Jones *et al.* (1997) and Mills *et al.* are viewed as the same as the instantly claimed vaccine formulation and method. Since the prior art vaccine formulation is structurally the same as the formulation recited in the instant claims and since the prior art method of parenteral administration of the vaccine formulation is the same as the instantly claimed method, the prior art formulation and the method are expected to, or necessarily result in the same effects, i.e., induction of a TH1 polarized immune response to the *B. pertussis* antigen. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of inducing a Th1 predominant immune response to a *B. pertussis* antigen in order to elicit Th1 cellular protective immunity to *B. pertussis* infection, since the art has recognized the central or critical need for inducing a Th1 protective immune response against *B. pertussis* infection as explicitly taught by Mills *et al.* Substitution one microbial antigen with another, art-known microbial antigen which has been demonstrated in the art to induce elevated IgG immune response on parenteral administration with PLG microparticles would have been obvious to a skilled artisan and would have brought about similarly effective immune responses, absent evidence to the contrary.

Claims 1, 5, 15 and 19 are *prima facie* obvious over the prior art of record.

17) Claims 1-6 and 15-19 are rejected under 35 U.S.C § 103(a) as being unpatentable over Jones *et al.* (*Vaccine* 1: 675-681, 1995) (Jones, 1995) in view of Nixon *et al.* (*Vaccine* 14: 1523-1530, 1996) and Tice *et al.* (US 6,024,983, already of record) or O'Hagan (*J. Pharm. Pharmacol.* 49: 1-10, 1997, already of record).

The reference of Tice *et al.* is used in this rejection, because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

Jones *et al.* (1995) teach a method of inducing antigen-specific serum IgG and protective immune responses in mice by intraperitoneal administration of *Bordetella pertussis* fimbrial

antigen entrapped or encapsulated in poly(lactide-co-glycolide) microspheres suspended in PBS (i.e., pharmaceutically acceptable carrier). The PLG (i.e, biodegradable polymer) microspheres in the formulation has a mean diameter of 24 micrometer (see title; abstract; section 'Immunisation'; Figure 3; page 678, full paragraph in left column and the paragraph bridging left and right columns). The antigen encapsulated microparticles are formed using a solvent evaporation method (see third full paragraph in the left column on page 676).

Jones *et al.* (1995) do not disclose the use of microparticles less than 5 or 3 micrometer in size in at least 50% quantity.

However, Nixon *et al.* provide the motivation for one skilled in the art to use smaller microparticles, i.e., less than 500 nm in size, to entrap a microbial antigen for parenteral administration in a mammalian subject. The teachings of Nixon *et al.* are explained above. Nixon *et al.* expressly teach that an encapsulated antigen composition comprising poly(lactide-co-glycolide) polymers sized <500 nm elicited a better cytotoxic T cell activity (CTL) compared to the composition comprising the antigen entrapped in larger sized microparticles (see abstract; and page 1524, right column under 'Immunization and *in vitro* CTL stimulation').

Similarly, Tice *et al.* disclose a method of administering to a subject subcutaneously, intramuscularly or intraperitoneally, microspheres encapsulated with a bacterial antigen to elicit a systemic IgG anti-toxin response. See Examples 1 and 2. The microparticles contain poly(DL-lactide-co-glycolide) (DLPG) having a size less than approximately 10 micrometers (see abstract). Tice *et al.* expressly teach that antigens that are used for encapsulation can be antigens from *Bordetella pertussis* (see claims 12, 25 and 38; and column 6, lines 30-34). Tice *et al.* teach microparticles prepared using PVA solvent and solvent evaporation process (see column 7, first full paragraph). In particular, Tice *et al.* disclose the advantages of using small microcapsules by stating that small microcapsules "preferably less than 5 micrometers, or more preferably 1 to 5 micrometers, potentiate the primary response (without the need of an adjuvant) because the small microcapsules are efficiently recognized and taken up by macrophages" (see column 17, last paragraph). Thus, Tice *et al.* expressly disclose that the use of small microcapsules, preferably 1 to 5 micrometers which get engulfed by macrophages, obviates the need for immunopotentiators (see column 22, second full paragraph).

O'Hagan (1997) teaches that biodegradable microparticles <5 micrometers act as effective vaccine adjuvants. O'Hagan (1997) teaches that smaller PLG microparticles, <10 micrometer in size (i.e., inclusive of those <5 micrometer in size) are significantly more immunogenic than larger microparticles and exert an adjuvant effect on cell-mediated immunity and induction of cytotoxic T-cell responses after systemic administration (see abstract; and page 6, first full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Jones' (1995) 24 micrometer-sized PLG microparticles with Nixon's PLG microparticles that are less than 500 nm in size to produce the formulation and the method of the instant invention, with a reasonable expectation of success. The induction of a T_H1 polarized immune response by the prior art vaccine in the method disclosed is implicit from the teaching of Jones *et al.* (1995) as modified by Nixon *et al.* Although the prior art references do not expressly recite the induction of a T_H1 polarized immune response by the vaccine in the disclosed method, the vaccine formulation and the method of Jones *et al.* (1995) as modified by Nixon *et al.* are viewed as the same as the instantly claimed vaccine formulation and method. Since the prior art vaccine formulation is structurally the same as the formulation recited in the instant claims and since the prior art method of parenteral administration of the vaccine formulation is the same as the instantly claimed method, the prior art formulation and the method are expected to, or necessarily result in the same effects, i.e., induction of a T_H1 polarized immune response to the antigen. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of eliciting a better CTL response as taught by Nixon *et al.*, or advantageously exerting an adjuvant effect on cell-mediated immunity and induction of cytotoxic T-cell responses as taught by O'Hagan (1997), or for efficient recognition by macrophages and for obviating the need for immunopotentiator as taught by Tice *et al.*

Claims 1-6 and 15-19 are *prima facie* obvious over the prior art of record.

18) Claims 15 and 20 are rejected under 35 U.S.C § 103(a) as being unpatentable over Nixon *et al.* (*Vaccine* 14: 1523-1530, 1996) as evidenced by Rook *et al.* (US 6,056,964) and in view of Jones *et al.* (*J. Biotechnol.* 44: 29-36, 1996, already of record).

The teachings of Nixon *et al.* as evidenced by Rook *et al.* are explained above which do

not disclose a vaccine composition having microparticles with at least two subpopulations of microparticles comprising different antigens.

However, as set forth above, Nixon *et al.* expressly suggest having in a vaccine composition microparticles prepared from combinations of polymers designed to degrade at different rates after immunization (see page 1530, second full paragraph). Nixon *et al.* also expressly teach that microparticles can be used to deliver a mixture of multiple immunogens in a single shot (see page 1529, left column, lines 3-6).

The concept of using combined PLG encapsulated antigens was well known in the art. Jones *et al.* (1996) taught the possibility of combining vaccine components by individually mixing PLG encapsulated antigens. Jones *et al.* (1996) taught that this might overcome the problems of perturbations in the immune responses that have been observed during the development of combination vaccines for the simultaneous administration of immunogens from the same syringe. Jones *et al.* (1996) further disclosed that formation of antigens in polymers of different compositions and therefore, different decay rates would have the effect of programming primary and secondary doses into a single administration. Jones *et al.* (1996) taught the application of PLG microencapsulation of antigens for combination of vaccine components and stated that combination of vaccines comprising any number of antigens could be tailored to meet any requirement (see page 30, right column, lines 7-25).

It would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to use two subpopulations of Nixon's microparticles and entrap more than one antigen in these microparticles to produce the composition of the instant invention, with a reasonable expectation of success, because Jones *et al.* (1996) expressly teach that PLG microcapsules comprising any number of antigens can be combined to produce encapsulated combination vaccines, and Nixon *et al.* expressly suggest the use of combinations of polymers designed to degrade at different rates after immunization and the use of microparticles to deliver a mixture of multiple immunogens. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of effectively and advantageously programming primary and secondary doses having different decay rates in a single composition as taught by Jones *et al.* (1996) and for delivering a mixture of multiple immunogens in a single shot as

taught by Nixon *et al.*

Claims 15 and 20 are *prima facie* obvious over the prior art of record.

Remarks

19) Claims 1-6 and 15-20 stand rejected.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER